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| 10/763,362   | 01/23/2004  | Mark William Bodmer  | 674525-2008                 | 7568                   |
| 20999 7590 07/16/2007<br>FROMMER LAWRENCE & HAUG<br>745 FIFTH AVENUE- 10TH FL.<br>NEW YORK, NY 10151 |             |                      |                             |                        |
|  |             |                      | EXAMINER<br>HUYNH, PHUONG N |                        |
|  |             |                      | ART UNIT<br>1644            | PAPER NUMBER           |
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

|                              |                               |                               |  |
|------------------------------|-------------------------------|-------------------------------|--|
| <b>Office Action Summary</b> | Application No.<br>10/763,362 | Applicant(s)<br>BODMER ET AL. |  |
|                              | Examiner<br>Phuong Huynh      | Art Unit<br>1644              |  |

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE three MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 02 February 2007.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1,2,8,18-24 and 29-35 is/are pending in the application.
- 4a) Of the above claim(s) 30,32 and 33 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1,2,8,18-24,29,31,34 and 35 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- |  |   |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)   | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)                       | 5) <input type="checkbox"/> Notice of Informal Patent Application                       |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)<br>Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____  |

### DETAILED ACTION

1. Upon reconsideration, The Final Rejection mailed May 4, 2007 is hereby withdrawn. A new Office Action is followed.
2. Claims 1-2, 8, 18-24 and 29-35 are pending.
3. Claims 30, 32 and 33 stand withdrawn from further consideration by the examiner, 37 C.F.R. 1.142(b) as being drawn to non-elected inventions.
4. In view of the amendment filed 2/2/07, the following rejections remain.
5. The following is a quotation of the first paragraph of 35 U.S.C. 112:  
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.
6. Claims 1-2, 8, 18-24, 29, 31 and 34-35 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling only for (1) a conjugate comprising a targeting protein and a human Notch ligand or a fragment thereof wherein the targeting protein is a bacterial superantigen that binds to the an MHC class II molecule on antigen presenting cell (APC) selected from the group consisting of Staphylococcal enterotoxin (SE), Streptococcal enterotoxin (SPE) and wherein the human Notch ligand is selected from the group consisting of human delta 1 comprising SEQ ID NO: 40, human Delta 3 comprising the amino acid sequence of SEQ ID NO: 41, human Delta 4 comprising the amino acid sequence of SEQ ID NO: 42, human Jagged 1 comprising the amino acid sequence of SEQ ID NO: 43, Jagged 2 comprising the amino acid sequence of SEQ ID NO: 44, or a human Notch ligand fragment selected from the group consisting of the amino sequence of SEQ ID NO: 25, SEQ ID NO: 29, SEQ ID NO: 32, SEQ ID NO: 36, SEQ ID NO: 38 and SEQ ID NO: 39 wherein the fragment binds to Notch receptor and retains Notch signaling activity, (2) a fusion protein comprising a targeting protein and a human Notch ligand or a fragment thereof wherein the targeting protein is a bacterial superantigen that binds to the an MHC class II molecule on antigen presenting cell (APC) selected from the group consisting of Staphylococcal enterotoxin (SE), Streptococcal enterotoxin (SPE) and wherein the

human Notch ligand is selected from the group consisting of human delta 1 comprising SEQ ID NO: 40, human Delta 3 comprising the amino acid sequence of SEQ ID NO: 41, human Delta 4 comprising the amino acid sequence of SEQ ID NO: 42, human Jagged 1 comprising the amino acid sequence of SEQ ID NO: 43, Jagged 2 comprising the amino acid sequence of SEQ ID NO: 44, or a human Notch ligand fragment selected from the group consisting of the amino sequence of SEQ ID NO: 25, SEQ ID NO: 29, SEQ ID NO: 32, SEQ ID NO: 36, SEQ ID NO: 38 and SEQ ID NO: 39 wherein the fragment binds to Notch receptor and retains Notch signaling activity, (3) the conjugate or fusion protein mentioned above wherein the Staphylococcal enterotoxin is selected from the group consisting of SEA, SEB, SEC, SED, SEE and She, (4) the conjugate or fusion protein mentioned above wherein the superantigen is Toxic Shock syndrome toxins (TSST-1), (5) the conjugate or fusion protein mentioned above wherein the Streptococcal enterotoxin is selected from the group consisting of SPEA, SPEC and SSA, and (6) the conjugate or fusion protein mentioned above wherein the human Notch ligand or fragment thereof contains a Notch ligand DSL domain and at least one EGF-like domain, **does not** reasonably provide enablement for any conjugate or fusion protein as set forth in claims 1-2, 8, 18-24, 29, 31 and 34-35. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

The claims encompass (1) any conjugate comprising a first sequence and a second sequence wherein the first sequence *comprises* any protein which binds to any antigen presenting cell (APC), and wherein the second sequence *comprises* any Notch ligand or any fragment thereof which retains Notch signaling activity, (2) any fusion comprising a first sequence and a second sequence wherein the first sequence comprises any protein which binds to any antigen presenting cell (APC), and wherein the second sequence comprises any Notch ligand or any fragment thereof which retains Notch signaling activity, (3) any conjugate comprising a first

sequence and a second sequence wherein the first sequence comprises any protein which binds to an MHC class II molecule, and wherein the second sequence comprises any Notch ligand or any fragment thereof which retains Notch signaling activity, (4) any conjugate comprising a first sequence and a second sequence wherein the first sequence comprises any superantigen, any superantigen from any bacterial or any viral origin or any derivative therefrom and wherein the second sequence comprises any Notch ligand or any fragment thereof which retains Notch signaling activity, (5) any conjugate comprising a first sequence and a second sequence wherein the first sequence comprises the MHC class II binding domain of any superantigen, and wherein the second sequence *comprises* any Notch ligand or any fragment thereof which retains Notch signaling activity, (6) any conjugate comprising a first sequence and a second sequence wherein the first sequence *comprises* superantigen wherein the superantigen is a Staphylococcal enterotoxin (SE) such as the ones recited in claims 22-24, and wherein the second sequence *comprises* any Notch ligand or any fragment thereof which retains Notch signaling activity, (7) any fusion protein prepared by (a) transforming a host cell with an expression vector comprising a polynucleotide sequence encoding the fusion protein comprising a first sequence and a second sequence wherein the first sequence *comprises* any protein which binds to any antigen presenting cell (APC), and wherein the second sequence *comprises* any Notch ligand or any fragment thereof which retains Notch signaling activity, (8) a composition comprising any conjugate comprising a first sequence and a second sequence wherein the first sequence *comprises* any protein which binds to any antigen presenting cell (APC), and wherein the second sequence *comprises* any Notch ligand or any fragment thereof which retains Notch signaling activity and a pharmaceutically acceptable carrier, (9) any conjugate comprising any first sequence and any second sequence wherein the first sequence comprises any protein which binds to any antigen presenting cell (APC), and wherein the second sequence is any protein for activation of any T cell costimulatory molecule, (4) any conjugate comprising any first sequence and any second sequence wherein the first sequence comprises any protein which binds to any antigen presenting cell (APC), and wherein the second sequence is any protein for Notch signaling transduction, (5) any conjugate comprising any first sequence and any second sequence wherein the first sequence comprises any protein which binds to any antigen presenting cell (APC), and wherein the second sequence is any Notch ligand, or any second sequence derived from any Delta or any Serrate, (6) any conjugate comprising any first sequence and any second sequence wherein the first sequence comprises any protein which binds to any antigen presenting cell (APC), and wherein the second

sequence is any protein that upregulates expression of any Notch, any protein that upregulates any activity of any Notch, any protein that upregulates any Notch signaling pathway, (7) any conjugate comprising any first sequence and any second sequence wherein the first sequence is any protein which binds to any antigen presenting cell (APC) surface molecule, and wherein the second sequence comprises any protein which modulates such as stimulates or inhibits which T cell signaling pathway, (8) any conjugate comprising any first sequence and any second sequence wherein the first sequence is any protein which binds to antigen presenting cell (APC) surface MHC class II molecule, and wherein the second sequence comprises any protein which modulates such as stimulates or inhibits which T cell signaling pathway, and (9) any conjugate comprising any first sequence and any second sequence wherein the first sequence is any protein which binds to any antigen presenting cell (APC) surface molecule, and wherein the second sequence comprises any protein which modulates such as stimulates or inhibits which T cell signaling pathway wherein the first sequence is any superantigen, any derivative thereof, any bacterial superantigen, any derivative of any bacterial superantigen, any viral superantigen, any derivative of any viral superantigen, any first sequence "comprises" the MHC class II binding domain of any superantigen, any superantigen is a staphylococcal enterotoxin (SE) selected from the group consisting of SEA, SEB, SEC, SEE, and SHE, Toxic Shock syndrome toxins (TSST-1), Streptococcal enterotoxin (SPE) selected from the group consisting of SPEA, SPEC, and SSA for activating or inhibiting any T cell signaling pathways in treating any diseases.

The only disclosed use of any conjugate mentioned above is for modulating, i.e., inhibiting or stimulating any T cell signaling pathways, upregulating expression of any Notch, upregulating any activity of any Notch signaling pathway, upregulating expression of any Notch ligand, upregulating any activity of any Notch ligand or and downstream component of any Notch signaling pathway for treating any diseases (see specification pages 30-34).

The specification discloses only a conjugate comprising a MHC class II binding domain of superantigen TSST1 consisting of SEQ ID NO: 45 as shown at page 41 or Figure 7 conjugated to a Notch ligand Jagged 1 as disclosed on page 66-67 wherein the superantigen TSST1 binds to major histocomplex class II antigen expressed on antigen presenting cell (APC) and wherein the Notch ligand binds to Notch. However, none of the conjugate or fusion protein has been demonstrate to have any biological activity. There is a lack of in vivo working examples demonstrating that any conjugate or fusion protein mentioned above when binds to MHC class II molecule expressed on APC and any Notch receptor on T cells upregulates which Notch receptor

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expression, or upregulates which activity of which Notch receptor, or affecting which downstream component of Notch signaling pathway. Let alone treating any diseases.

Enablement is not commensurate with how to make and use any conjugate or fusion protein mentioned above comprising any first sequence and any second sequence wherein the first sequence comprises any protein which binds to any antigen presenting cell (APC), and wherein the second sequence comprises any Notch ligand or any fragment thereof which retains Notch signaling activity. This is because “a first sequence comprising a protein” and second sequence such as any Notch ligand fragment that retains Notch signaling activity without the amino acid sequence has no structure, much less function. The specification as filed does not teach which “fragment of which Notch Ligand” retains Notch signaling activity. The specification does not teach how to make and use any Notch ligand fragment that retains which Notch ligand signaling transduction activity in T cells. There is a lack of guidance as to which amino acids within the full-length sequence of which Notch ligand to be substituted, deleted, added and/or combination thereof such that the Notch ligand still maintains its structure and retains which activity when binds to which Notch receptor, in turn, signaling by modulating, i.e. inhibiting or stimulating which T cell signaling pathway.

With regard to superantigen “derivative therefrom, the term “derivative” encompasses any modification such as substitution, deletion, addition and/or any combination thereof. The specification as filed does not adequately teach any and all superantigens, much less any and all “derivative” thereof such that the superantigen in the first sequence of the conjugate or fusion protein still binds to MHC class II molecule on the antigen presenting cell such as dendritic cells, B cells, and macrophage. It is well known in the art that molecules having highly diverse structural biochemical properties can function as an analog. However, Huang et al (Pharmacol. Therapeutics 86: 201-205, 2000; PTO 892) reviews the daunting task faced by the skilled artisan in developing molecular regulators of protein-protein interactions and notes that the process required long periods of trial and error testing before such suitable compounds could be developed (see page 202, Introduction, in particular). Thus the structure of such analog cannot be readily envisioned by one skilled in the art based upon the guidance provided in the specification.

With regard to “first sequence is a protein which binds to APC surface molecule”, given the unlimited number of sequence, it is unpredictable which sequence binds to which cell surface molecule on which APC, dendritic cells, macrophage, B cells etc. Likewise, there is insufficient

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guidance as to which amino acid sequence of which protein from any and all superantigens of bacterial or viral antigen binds to MHC class II surface molecule on APC.

Stryer *et al* teach that a protein is highly dependent on the overall structure of the protein itself and that the primary amino acid sequence determines the conformational of the protein (See enclosed appropriate pages).

Ngo *et al* teach that the amino acid positions within the polypeptide/protein that can tolerate change such as conservative substitution or no substitution, addition or deletion which are critical to maintain the protein's structure/function will require guidance (See Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495).

The Notch signaling in T cell function has a tremendous number of both upstream and downstream effector molecules. The state of the art as summarized by Tsukumo et al (J Immunology 173: 7109-7113, 2004; PTO 892) is such that there are conflicting evidence for Notch signaling on mature T cell activation and differentiation (see abstract, page 7112, in particular). In mammals, there are four Notch receptors (Notch 1-4) and at least five Notch ligands (Jagged 1 and 2, Delta1, 3 and 4) are identified (see page 7109, col. 2, in particular). However, the detailed relationship between Notch signaling and T cells activation/differentiation has not been established (see page 7112, col. 1, in particular). The receptors and ligands can interact with each and the expression pattern of each molecule is not restricted, which makes it difficult to analyze the role of Notch systems in mature T cell differentiation/activation and how T cells utilize different Notch molecules to regulate their own differentiation. Accordingly, an undue amount of experimentation would be required to determine how to practice the claimed invention.

For these reasons, it would require undue experimentation of one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

Applicants' arguments filed 2/2/07 have been fully considered but are not found persuasive.

Applicants' position is that the claims have been amended. The sequences that bind to an APC are not unpredictable. To the contrary, several of such molecules are described in the specification, for example at page 13, lines 5-21, such as antibodies to CD205 (DEC205), CD204, CD14, CD206, TLRs, Langerin (CD207), DC-SIGN (CD209), CD32, CD68, CD83, CD33, CD54 or BDCA-2,3,4. In addition, conventional protein binding assays can be used to determine whether a sequence binds to an APC. Such assays are well within the ordinary skill of the artisan and do not constitute undue experimentation.

In response, it is noted that the term "antibody" is not recited in any of the pending claims. The first sequence comprises a protein that binds to APC could be a ligand or a receptor or an antibody or a superantigen from any bacteria or any virus or any derivative of any superantigen thereof. It is not clear as to the binding specificity of such protein without the structure associated with such protein. Further, the term "comprises" expands the first sequence to include additional amino acids to either or both ends. There is insufficient guidance as to which amino acids to be added such that it maintains its three dimensional structure and binding to which protein on the surface of an antigen presenting cells.

With regard to second sequence comprises a Notch ligand or fragment thereof or a Notch ligand DSL domain and at least one EGF-like domain in the claimed conjugate or fusion protein, the specification discloses only Notch ligand from only human such as delta 1, Delta 3, Delta 4, Jagged 1 and Jagged 2 comprising the amino acid sequence of SEQ ID NO: 40, 41, 42, and 43 and 44, respectively, see page 38. The specification discloses the DSL domains from Drosophila and human Notch ligands consisting of the amino acid sequence of SEQ ID NO: 24-39 as shown in Figure 9. Other than the specific Notch ligand from human and the specific Notch ligand fragment containing the DSL domains mentioned above that retains the ability to bind to Notch receptor and Notch signaling activity, there is insufficient guidance as to the structure of any and all other Notch ligand and any and all DSL domains for the claimed conjugate or fusion protein without the amino acid sequence. Further, the term "comprises" expands the second sequence in the claimed conjugate or fusion protein to include additional amino acids at either or both ends. There is a lack of guidance as to which amino acids to be added such that the Notch ligand or fragment thereof still retains its binding specificity to the Notch receptor, in turn, effective for stimulating or inhibiting its signaling activity *in vivo*.

With regard to superantigen “derivative therefrom, the term “derivative” encompasses any modification such as substitution, deletion, addition and/or any combination thereof. The specification as filed does not adequately teach any and all superantigens, much less which amino acid within the full-length sequence of any and all superantigen to be substituted, deleted, added and/or combination thereof such that the “derivative” of the superantigen in the first sequence of the conjugate or fusion protein still binds to MHC class II molecule on the antigen presenting cell such as dendritic cells, B cells, and macrophage. It is well known in the art that molecules having highly diverse structural biochemical properties can function as an analog. However, Huang et al (Pharmacol. Therapeutics 86: 201-205, 2000; PTO 892) reviews the daunting task faced by the skilled artisan in developing molecular regulators of protein-protein interactions and notes that the process required long periods of trial and error testing before such suitable compounds could be developed (see page 202, Introduction, in particular). Thus the structure of such analog cannot be readily envisioned by one skilled in the art based upon the guidance provided in the specification.

7. Claims 1-2, 8, 18-24, 29, 31 and 34-35 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** of any conjugate or any fusion protein comprising any first sequence and any second sequence wherein the first sequence comprises any protein which binds to any antigen presenting cell (APC), and wherein the second sequence is any Notch ligand or any fragment thereof which retains Notch signaling activity, (2) any and all derivative of any superantigen for the claimed conjugate, (3) any conjugate or any fusion protein comprising any first sequence and any second sequence wherein the first sequence comprises any protein which binds to any antigen presenting cell (APC), and wherein the second sequence comprises any Notch ligand DSL domain and at least one EGF-like domain and wherein the second sequence retains Notch signaling activity, and (4) any conjugate or any fusion protein comprising any first sequence and any second sequence wherein the first sequence comprises any protein which binds to an APC surface molecule such as the ones recited in claim 35, and wherein the second sequence is any Notch ligand or any fragment thereof which

retains signaling activity for activating or inhibiting any T cell signaling pathways in treating any diseases.

The specification discloses only a conjugate comprising a MHC class II binding domain of superantigen TSST1 consisting of SEQ ID NO: as shown at page 41 or Figure 7 conjugated to a Notch ligand Jagged 1 as disclosed on page 66-67 wherein the superantigen TSST1 binds to major histocomplex class II antigen expressed on antigen presenting cell (APC) and wherein the Notch ligand binds to Notch.

With the exception of the specific fusion or conjugate mentioned above, there is insufficient written description about the structure associated with function of any and all protein comprises a first sequence wherein the first sequence comprises any protein which binds to any antigen presenting cell and a second sequence wherein the second sequence "comprises" any Notch ligand or any Notch ligand fragment thereof which retains Notch signaling activity in all the claimed conjugates or fusion protein. This is because a "first sequence" and a "second sequence" in the claimed conjugate or fusion protein without the amino acid sequence has no structure, much less function. The first sequence comprises a protein that binds to APC could be a ligand or a receptor or an antibody or a superantigen from any bacteria or any virus or any derivative of any superantigen thereof. It is not clear as to the binding specificity of such protein without the structure associated with such protein. Further, the term "comprises" expands the first sequence to include additional amino acids to either or both ends. There is inadequate written description as to which amino acids to be added such that it maintains its there dimensional structure and binding to which protein on the surface of an antigen presenting cells.

With regard to second sequence comprises a Notch ligand or fragment thereof or a Notch ligand DSL domain and at least one EGF-like domain in the claimed conjugate or fusion protein, the specification discloses only Notch ligand from only human such as delta 1, Delta 3, Delta 4, Jagged 1 and Jagged 2 comprising the amino acid sequence of SEQ ID NO: 40, 41, 42, and 43 and 44, respectively, see page 38. The specification discloses the DSL domains from Drosophila and human Notch ligands consisting of the amino acid sequence of SEQ ID NO: 24-39 as shown in Figure 9. Other than the specific Notch ligand from human and the specific Notch ligand fragment containing the DSL domains mentioned above that retains the ability to bind to Notch receptor and Notch signaling activity, the structure of any and all other Notch ligand and any and all DSL domains for the claimed conjugate or fusion protein is not adequately described without the amino acid sequence. Further, the term "comprises" expands the second sequence in the

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claimed conjugate or fusion protein to include additional amino acids at either or both ends. The amino acids to be added such that the Notch ligand or fragment thereof still retains its binding specificity to the Notch receptor, in turn, effective for stimulating or inhibiting its signaling activity *in vivo* are not adequately described.

With regard to superantigen "derivative therefrom, the term "derivative" encompasses any modification such as substitution, deletion, addition and/or any combination thereof. The specification as filed does not adequately describe any and all superantigen from any bacterial or any virus, much less any and all "derivative" thereof such that the superantigen in the first sequence of the conjugate or fusion protein still binds to MHC class II molecule on the antigen presenting cell such as dendritic cells, B cells, macrophage. Thus the structure of such derivative cannot be readily envisioned by one skilled in the art based upon the guidance provided in the specification.

The specification discloses only one conjugate comprising only human Notch ligand fused to TSST-1, of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species of conjugate or fusion protein to describe the genus for the claimed conjugate. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co.* 43 USPQ2d 1398; *University of Rochester v. G.D. Searle & Co.*, 69 USPQ2d 1886 (CA FC2004).

Applicant is directed to the Final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Applicants' arguments filed 2/2/07 have been fully considered but are not found persuasive.

Applicants' position is that the claims have been amended. The sequences bind to an APC is not unpredictable. To the contrary, several of such molecules are described in the specification, for example at page 13, lines 5-21, such as antibodies to CD205 (DEC205), CD204, CD14, CD206, TLRs, Langerin (CD207), DC-SIGN (CD209), CD32, CD68, CD83, CD33, CD54 or BDCA-2,3,4. In addition, conventional protein binding assays can be used to determine whether a sequence binds to an APC. Such assays are well within the ordinary skill of the artisan and do not constitute undue experimentation.

In response, it is noted that the term "antibody" is not recited in any of the pending claims. The specification discloses only a conjugate comprising a MHC class II binding domain

of superantigen TSST1 consisting of SEQ ID NO: as shown at page 41 or Figure 7 conjugated to a Notch ligand Jagged 1 as disclosed on page 66-67 wherein the superantigen TSST1 binds to major histocomplex class II antigen expressed on antigen presenting cell (APC) and wherein the Notch ligand binds to Notch.

With the exception of the specific fusion or conjugate mentioned above, there is insufficient written description about the structure associated with function of any and all protein comprises a first sequence wherein the first sequence comprises any protein which binds to any antigen presenting cell and a second sequence wherein the second sequence "comprises" any Notch ligand or any Notch ligand fragment thereof which retains Notch signaling activity in all the claimed conjugates or fusion protein. This is because a "first sequence" and a "second sequence" in the claimed conjugate or fusion protein without the amino acid sequence has no structure, much less function. The first sequence comprises a protein that binds to APC could be a ligand or a receptor or an antibody or a superantigen from any bacteria or any virus or any derivative of any superantigen thereof. It is not clear as to the binding specificity of such protein without the structure associated with such protein. Further, the term "comprises" expands the first sequence to include additional amino acids to either or both ends. There is inadequate written description as to which amino acids to be added such that it maintains its three dimensional structure and binding to which protein on the surface of an antigen presenting cells.

With regard to second sequence comprises a Notch ligand or fragment thereof or a Notch ligand DSL domain and at least one EGF-like domain in the claimed conjugate or fusion protein, the specification discloses only Notch ligand from only human such as delta 1, Delta 3, Delta 4, Jagged 1 and Jagged 2 comprising the amino acid sequence of SEQ ID NO: 40, 41, 42, and 43 and 44, respectively, see page 38. The specification discloses the DSL domains from *Drosophila* and human Notch ligands *consisting* of the amino acid sequence of SEQ ID NO: 24-39 as shown in Figure 9. Other than the specific Notch ligand from human and the specific DSL domains mentioned above, the structure of any and all other Notch ligand and DSL domains for the claimed conjugate or fusion protein is not adequately described. Further, the term "comprises" expands the second sequence in the claimed conjugate or fusion protein to include additional amino acids at either or both ends. The amino acids to be added to such undisclosed Notch ligand or fragment thereof still retains its binding specificity to Notch receptor, in turn, effective for stimulating or inhibiting its signaling activity *in vivo* are not adequately described.

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With regard to superantigen “derivative therefrom, the term “derivative” encompasses any modification such as substitution, deletion, addition and/or any combination thereof. The specification as filed does not adequately describe any and all superantigen, much less any and all “derivative” thereof such that the superantigen in the first sequence of the conjugate or fusion protein still binds to MHC class II molecule on the antigen presenting cell such as dendritic cells, B cells, macrophage. Thus the structure of such derivative cannot be readily envisioned by one skilled in the art based upon the guidance provided in the specification.

The specification discloses only one conjugate comprising only human Notch ligand fused to TSST-1, of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species of conjugate or fusion protein to describe the genus for the claimed conjugate. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co.* 43 USPQ2d 1398; *University of Rochester v. G.D. Searle & Co.*, 69 USPQ2d 1886 (CA FC2004).

8. The following new grounds of objection and rejections are necessitated by the amendment filed 2/2/07.
9. Claim 8 is objected to because the plural “ligands” is not consistent with the singular “ligand” in base claim 1.
10. The following is a quotation of the second paragraph of 35 U.S.C. 112:  
The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.
11. Claims 2 and 29 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term “A conjugate prepared by transforming a host cell...” in claim 29 is ambiguous and indefinite because transforming host cell produces fusion protein, NOT a conjugate. A conjugate involves chemical coupling of two proteins, see specification at page 26, lines 11-27. The specification at page 24-25 discloses the *fusion polypeptide* or fusion protein is produced by transforming host cell with an expression vector comprising a polynucleotide encoding the fusion polypeptide to produce the fusion protein.

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12. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

13. Claims 1-2, 8, 29, 31, and 34-35 are rejected under 35 U.S.C. 102(b) as being anticipated by WO 98/20142 publication (published May 14, 1998; PTO 1449).

The WO 98/20142 publication teaches a protein comprising a first sequence operably linked to a second sequence wherein the first sequence is a protein such as human IgG1-Fc that binds to an antigen presenting cell (APC) and a second sequence such as the extracellular domain of Notch ligand selected from Delta or Serrate or fragments or derivatives or analogs thereof (see claims 4-6, 15-17 of the WO 98/20142 publication, pages 8 and 16, in particular). The Fc of the reference protein inherently binds to the APC cell surface molecule such as the CD32, which is the low affinity Fcγ receptor. The reference extracellular domain of Notch ligand fusion protein retains the ability to bind to Notch and inhibits its signaling activity since the notch ligand contains DSL domain which is the 20-22 amino acids at the amino terminus of the protein and between 3-8 EGF-like repeats on the extracellular domain (see page 4, lines 20-22, page 2, line 12-14, in particular). The WO 98/20142 publication teaches a composition comprising the reference fusion protein (see page 11, line 21-26, in particular). The reference protein is produced by transforming a host cell such as *E coli* or COS cell with an expression vector such as pIG-1 comprising the nucleic acid encoding the reference fusion protein and culturing the host cell under conditions to produce the reference protein (see page 16, Example 2, in particular). Thus, the reference teachings anticipate the claimed invention.

14. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

15. This application currently names joint inventors. In considering Patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was

commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

16. Claims 1 and 18-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 98/20142 publication (published May 14, 1998; PTO 1449) in view of WO 98/26747 publication (June 25, 1998; PTO 1449).

The teachings of the WO 98/20142 publication have been discussed supra. The WO 98/20142 publication teaches the Notch ligand fusion protein is useful for mediating Notch signaling activity by induction of tolerance for treating allergy, asthma, and infectious disease (see abstract, in particular).

The invention in claim 18 differs from the teachings of the reference only in that the conjugate wherein the first sequence is a protein which binds to an MHC class II molecule instead of Fc receptor CD32.

The invention in claim 19 differs from the teachings of the reference only in that the conjugate wherein the first sequence is a superantigen, or is derived therefrom.

The invention in claim 20 differs from the teachings of the reference only in that the conjugate wherein the first sequence is a superantigen of bacterial origin.

The invention in claim 21 differs from the teachings of the reference only in that the conjugate wherein the first sequence comprises the MHC class II binding domain of the superantigen.

The invention in claim 22 differs from the teachings of the reference only in that the conjugate wherein the first sequence is a superantigen Staphylococcal enterotoxin (SE) selected from the group consisting of SEA, SEB, SEC, SED, SEE and SEH.

The invention in claim 23 differs from the teachings of the reference only in that the conjugate wherein the first sequence is a superantigen is Toxic Shock syndrome toxins (TSST-1).

The invention in claim 24 differs from the teachings of the reference only in that the conjugate wherein the first sequence is a superantigen is a Streptococcal enterotoxin (SPE) selected from the group consisting of SPEA, SPEC and SSA.

The WO 98/26747 publication teaches a conjugate protein comprising a first protein such as bacterial superantigen selected from SEA, SEB, SEC, SED, SEE, TSST-1, SPE-A, SPE-B, or SPE-C that binds to the MHC class II on antigen presenting cell (see page 35, in particular) linked to a second sequence such as a tumor specific antigen such as MAGE-1, MAGE3, MART-1 (see claims 20-22 of WO 98/26747 publication, pages 10, page 22, in particular). The reference conjugate can be created as a fusion protein (see page 34, Example 2, in particular). The superantigen in the reference conjugate or fusion protein targets the tumor antigen to the antigen presenting cell expressing the MHC class II molecule (see page 9, in particular). The reference fusion protein is made by culturing host cell expressing the reference fusion protein (see abstract, claim 31 of the publication, in particular). The publication also teaches a pharmaceutical composition comprising the reference conjugate or fusion protein and pharmaceutical acceptable carrier such as buffered saline, (see claim 22 of the publication, page 36, 3<sup>rd</sup> paragraph, page 17, Pharmaceutical compositions and Their Preparation, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute Fc in the fusion protein comprising a Notch ligand or fragment thereof which retains Notch signaling activity as taught by the WO 98/20142 publication for bacterial superantigen selected from SEA, SEB, SEC, SED, SEE, TSST-1, SPE-A, SPE-B, or SPE-C that binds to the MHC class II on antigen presenting cell as taught by the WO 98/26747 publication. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because the WO 98/26747 publication teaches bacterial superantigen such as SEA, SEB, SEC, SED, SEE, TSST-1, SPE-A, SPE-B, or SPE-C is useful for targeting any antigen such as tumor antigen to the antigen presenting cell by binding to the MHC class II expressed on antigen presenting cell (see claims 20-22 of WO 98/26747 publication, pages 10, page 22, in particular). The WO 98/20142 publication teaches the Notch ligand fusion protein is useful for mediating Notch signaling activity by induction of tolerance for treating allergy, asthma, and infectious disease (see abstract, in particular).

17. No claim is allowed.

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18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phuong Huynh, PhD whose telephone number is (571) 272-0846. The examiner can normally be reached Monday through Thursday from 9:00 a.m. to 6:30 p.m. and alternate Friday from 9:00 a.m. to 5:30 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The IFW official Fax number is (571) 273-8300.
19. Any information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Phuong Huynh/

Patent Examiner

Technology Center 1600

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